ERJ Express. **Published on August 6, 2010 as doi: 10.1183/09031936.00089610**

A non-invasive algorithm to exclude precapillary pulmonary hypertension

Diana Bonderman, MD, Paul Wexberg, MD, Amadea M Martischnig, MD, Harald Heinzl, PhD*, Marie-Beatrice Lang, MS, Roela Sadushi, MD, Nika Skoro-Sajer, MD, Irene M Lang, MD

From the Department of Cardiology and the *Core Unit for Medical Statistics and Informatics, Medical University of Vienna, Austria

Bonderman – exclusion of precapillary PH

Total word count: 6 581

Conflicts of interest: none

Financial disclosures: none

This study received financial support from by the European Commission under the 6th Framework Programme (Contract No: LSHM-CT-2005-018725, PULMOTENSION, to IML). This publication reflects only the author´s views and the European Community is in no way liable for any use that may be made of the information contained therein.

This research was supported by the Austrian fellowship grant L 513-B11 (to DB), and the Hans und Blanca Moser Stiftung (to AMM).

Correspondence should be addressed to: Diana Bonderman MD, Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria, Tel: + 43 1 40 400 4614, Fax: + 43 1 40 400 4216, e-mail: diana.bonderman@meduniwien.ac.at

Abstract.

Background. Current guidelines recommend right heart catheterization (RHC) in symptomatic patients at risk of precapillary pulmonary hypertension (PH) with echocardiographic systolic pulmonary pressures (sPAP) ≥36mmHg. Growing awareness for PH, a high prevalence of postcapillary PH and the inability to distinguish between pre- and postcapillary PH by echocardiography have led to unnecessary RHCs. The aim of the present study was to assess whether standard non-invasive diagnostic procedures are able to safely exclude precapillary PH.

Methods. Data from 251 patients referred for clinical and echocardiographic suspicion of precapillary PH were used to develop a non-invasive diagnostic decision tree. Bootstrapping was applied for internal validation and a prospectively collected data set of 121 consecutive patients was utilized for temporal validation.

Results. According to the decision tree, patients were stratified by the presence or absence of an electrocardiographic right ventricular strain pattern (RVS) and serum NT-proBNP levels below and above 80pg/ml. In the absence of RVS and elevated NT-proBNP, none of the patients in the prospective validation cohort was diagnosed with precapillary PH by RHC. Compared with current indication for RHC that is mainly based on echocardiography, a combination with the diagnostic algorithm increased specificity to 19.3% (p=0.0009), while sensitivity remained 100%.

Conclusion. A diagnostic decision tree employing ECG and NT-proBNP on top of echocardiography helps recognize one false positive case per five patients referred with dyspnea and echocardiographic suspicion of PH, while not missing true precapillary PH.

Background.

Precapillary pulmonary hypertension (precapillary PH) is a severe condition leading to right heart failure and death within 2-3 years after diagnosis, if left untreated [1]. While idiopathic pulmonary arterial hypertension (PAH) is rare, associated forms of PAH [2] are more common and may be triggered by collagen vascular disease, appetite suppressants [3], HIV-infection [4], increased shear stress and hypoxia [2, 5-7]. A series of medical conditions, including infection, immune disorders, inflammatory bowel disease and permanent venous catheters [8, 9], predispose to chronic thromboembolic pulmonary hypertension (CTEPH) [10].

According to international guidelines [2] that were recently up-dated [11-13], invasive hemodynamic measurement by right heart catheterization (RHC) is recommended in patients with clinical suspicion of precapillary PH if systolic pulmonary arterial pressure (sPAP) by transthoracic echocardiography (TTE) ≥36mmHg. An invasively measured pulmonary capillary wedge pressure of 15mmHg has been used to discriminate between precapillary and postcapillary pulmonary pressure elevation that mostly occurs as a consequence of left-sided heart disease [14]. The growing awareness for PH, a high prevalence of postcapillary PH [15] and the inability of TTE to distinguish between pre- and postcapillary PH have necessitated invasive hemodynamic measurements for exclusion. Furthermore, Doppler echocardiography is frequently inaccurate in estimating sPAP [16]. Given a low specificity of PH symptoms and sPAP elevations by TTE, the decision to either proceed with RHC or withhold further invasive testing is a common clinical problem, especially in high-volume PH referral centers [17]. Although rare [18], complications of RHC may be ventricular tachyarrhythmia, vascular or ventricular perforation, bleeding, pneumothorax and even death [19]. However, a restrictive use of RHC may delay a timely diagnosis and treatment [20].

Apart from TTE, 12-lead electrocardiography (ECG), serum N-terminal brain natriuretic peptide (NT-proBNP) and lung function tests with blood gas analysis have been recommended in patients who present with dyspnea. Typical ECG signs of precapillary PH are right ventricular hypertrophy (RVH) and strain (RVS), and signs of right atrial dilation such as *p pulmonale*. The role of ECG for the diagnosis of PH has been investigated in a large American registry initiated in the early eighties. Rich and co-workers reported that electrocardiographic RVH was present in 87% and right axis deviation in 79% of patients with idiopathic PH [21]. Elevated serum NT-proBNP [22] and hypocapnia [23] have been established as independent markers of mortality in PH. However, the combined diagnostic use of these non-invasive tests has not been validated. Therefore, we tested the ability of standard non-invasive diagnostic procedures to correctly identify or exclude precapillary PH in patients referred for clinical suspicion of PH and echocardiographic sPAP ≥ 36mmHg. We used a retrospective data set of 251 consecutive individuals and constructed a simple non-invasive diagnostic algorithm. In a prospective temporal validation study enrolling 121 new consecutive patients, the incremental diagnostic value of the combined use of TTE, ECG and NT-proBNP over TTE alone was confirmed.

Methods.

Setting and study design.

The study was approved by the Ethics Committee of the Medical University of Vienna, and written informed consent was collected from prospectively enrolled patients. The study was performed at the Pulmonary Hypertension Unit of the Medical University of Vienna as a tertiary referral center for PH.

Retrospective study. Between January 2002 and April 2007, 462 patients were referred for the evaluation of PH. TTE, 12-lead ECG, serum NT-proBNP and lung function tests including partial pressure of carbon dioxide in arterial blood ($PaCO_2$) were performed upon admission in each patient. Patients with echocardiographic sPAP <36mmHg (n=80) were not considered for invasive hemodynamic assessment. Patients carrying pacemakers or implantable cardioverters/defibrillators (n=12) were excluded because of the inapplicability of standard ECG criteria. Seventy-one patients were excluded because of severe valvular disease, congenital malformations, and/or severely impaired left ventricular function. Of the 299 patients who were considered appropriate study candidates, 48 were excluded because of incomplete data, leaving 251 patients for analysis. Based on the invasive hemodynamic evaluation by RHC, the diagnosis "precapillary PH" or "no precapillary PH" was made.

Prospective study. For temporal validation of the diagnostic algorithm that had been constructed from the retrospective data set, we enrolled consecutive patients referred between June 2007 and October 2008. From a total of 222 individuals, 101 were excluded because of valvular heart disease (n=29), left ventricular dysfunction (n=8), congenital heart disease (n=8), pacemaker (n=17), and an echocardiographic sPAP

<36mmHg (n=30). In one patient NT-proBNP had not been determined and one patient died prior to a complete assessment. Seven patients refused to participate in the study. In the remaining 121 patients, non-invasive diagnostic procedures were performed in an outpatient setting. Based on the diagnostic algorithm, each patient was categorized as "precapillary PH excluded" or "precapillary PH likely". In a next step, all patients underwent invasive hemodynamic assessment by RHC. Based on these results, a diagnosis was made that served as the validation standard.

Transthoracic echocardiography.

All TTE studies were performed by board certified physicians in the echo laboratory of the Medical University of Vienna using high-end scanners, such as Siemens Acuson Sequoia and GE Vivid 5 and Vivid 7. The current standard in our echo lab are two observers. TTE studies were based on measurements that are broadly available and routinely used in the evaluation of patients with suspected PH.

Right ventricular dysfunction was diagnosed based on a visual assessment and on a tricuspid annular plane systolic excursion of less than 18mm. sPAP was calculated by adding estimated right atrial pressure to the tricuspid regurgitation pressure gradient. No contrast agents were used for enhancement of Doppler signals. Right atrial pressure was estimated based on the diameter and respiratory variation of the inferior vena cava [11].

Left ventricular hypertrophy was diagnosed if end-diastolic septal thickness in the apical 4-chamber view was ≥12mm.

Left ventricular diastolic dysfunction was diagnosed in the presence of a restrictive or pseudo-normal filling pattern and normal or only mildly abnormal left ventricular ejection fraction (LVEF>50%). A restrictive filling pattern was defined by an E/A waves ratio >2 and a deceleration time <150ms. A pseudo-normal filling pattern was

diagnosed, if E/A waves ratio and deceleration time were normal but changed to abnormal after Valsalva [24].

ECG.

Retrospective and prospective study. A 12-lead ECG was recorded according to clinical standards at a paper speed of 25mm/s. ECGs were analyzed by two cardiologists who were blinded to the clinical and echocardiographic data. ECG rulers and calipers were used. In case of disagreement, consensus was achieved between the two observers in a second reading. The following parameters were obtained: (a) presence or absence of sinus rhythm, (b) heart rate in beats per minute, (c) P-wave amplitude in milliVolts (mV) in lead II, (d) P-wave axis in degrees (°), (e) presence or absence of *p pulmonale* defined as a P-wave amplitude > 0.25mV, (f) electric heart axis in °, (g) right axis deviation defined as a QRS-axis >110°, (h) QRS width in ms, (i) presence or absence of bundle branch block defined as a QRS width >100ms, and stratification in right bundle branch block (RBBB) or left bundle branch block (LBBB), (j) the presence or absence of RVS pattern defined as ST-segment deviation and T-wave inversion in leads V1-V3 [25], (k) the presence or absence of left ventricular strain pattern defined as ST-segment deviation and T-wave inversions in leads V5 and V6, (l) QT-length in milliseconds (ms) and corrected QT-length (QTc) calculated by the Bazett-formula [26]. RVH was defined by a ratio of R and S in lead V1 >1.

Assessments.

A detailed medical history including medical conditions known to be associated with PH was taken [2, 5, 6, 27]. Associated conditions were collagen vascular disease, HIV infection, history of appetite suppressant intake, splenectomy, or ventriculo-atrial

shunt. In addition, exercise capacity measured by the distance in meters walked in six minutes and the modified New York Heart Association (NYHA) class [28] at presentation were determined in each patient.

Blood gas analysis was performed with an ABL 510 blood gas analyzer (Radiometer, Denmark).

Serum NT-proBNP was measured utilizing the Elecsys proBNP kit (Roche, Basel, Switzerland). Hemodynamic assessment by RHC included measurement of cardiac output utilizing both the Fick equation and the thermodilution method. "Precapillary PH" was diagnosed if mean pulmonary arterial pressure exceeded 25mmHg at rest, and pulmonary capillary wedge pressure was below 15mmHg [2].

Statistical analysis.

Statistical computations were performed with SPSS (version 15.0, SPSS Inc., Chicago, IL, USA) and SAS (version 9.1, SAS Institute Inc., Cary, NC, USA). Continuous variables were described with mean and standard deviations. Groups were compared with the unpaired t-test. Right-skewed variables were logarithmically transformed before testing. Nominal variables were described with counts and percentages, groups were compared with chi-squared or Fisher's exact test. Wilson's method was used to compute confidence intervals (CI) for single proportions. McNemar's test was used to compare sensitivities and specificities of diagnostic decision rules. All reported p-values are results of two-tailed tests, and p-values <0.05 were considered statistically significant.

Univariable logistic regression models were used to assess whether TTE, clinical and ECG variables allowed discriminating between "precapillary PH" and "no precapillary PH". Stepwise selection (forward search) within the three groups (TTE, clinical and ECG variables) yielded partially independent variable sets. The clinical and the ECG

variable sets were used to construct a diagnostic decision tree (Classification and Regression Tree (CART)) for "precapillary PH" versus "no precapillary PH" employing the CHAID (Chi-Squared Automatic Interaction Detection) method of SPSS and defining diagnostic branch points and terminal nodes. At each branch point a case will either branch to the left or to the right based on a test against a threshold predictor value, and will continue branching in subsequent nodes until a terminal node is reached.

Because of the prognostic implications of a delayed PAH diagnosis and treatment [1] a false negative diagnosis was assumed to have far more serious consequences than a false positive one. Therefore, the class assignment rule was chosen in a way that the percentage of false negative predictions did not exceed 4% (one out of 25) of the true positive cases.

To overcome the problem of overoptimistic results, both an internal and a temporal validation step were added [29]. Internal validation was based on the bootstrap approach [30] reporting an average of thirty bootstrap samples. Temporal validation was based on the prospective sample.

Results.

Characteristics of the retrospective patient cohort.

Patient characteristics are summarized in Table 1. According to RHC results, patients were classified as "precapillary PH" (n=187, 74.5%) or "no precapillary PH" (n=64, 25.5%). In the "precapillary PH" group, 49 patients were eventually diagnosed with idiopathic or familial PH, or PH associated with corrected or small (<2cm) uncorrected atrial septal defects, 2 patients had a history of anorexigen intake, 6 were HIV-positive, 10 female patients suffered from collagen vascular disease, 2 had PH in association with Osler's disease, 13 patients had underlying lung disease [31] and 97 patients had CTEPH, 7 had porto-pulmonary hypertension, and one patient suffered from pulmonary veno-occlusive disease. In the "no precapillary PH" group, 53 patients were diagnosed with postcapillary PH. Of those 42 patients suffered from PH due to left ventricular diastolic dysfunction (34 with systemic arterial hypertension and 10 with significant coronary artery disease). Nine patients with postcapillary hypertension suffered from PH due to lung disease and/or hypoxemia [32]. In 11 patients PH was excluded because mPAP was <25mmHg. Of those, one patient was diagnosed with pulmonary lymphangioleiomyomatosis, one patient had an isolated pulmonary AV-malformation, 2 patients had manifest hyperthyreoidism, 2 patients were diagnosed with unilateral pulmonary artery occlusion, 2 patients had atrial septal defect, and 3 patients had severe isolated tricuspid valve regurgitation.

There were no between-group differences with respect to demographic characteristics, including age and sex. Furthermore, no differences were encountered in the 6-minute walking distances or serum creatinine levels. However, statistically significant differences between "precapillary PH" and "no precapillary PH" were found in NYHA class, serum NT-proBNP, $PaCO_2$, associated medical

conditions, TTE parameters, such as sPAP, right ventricular function and diameter, left ventricular wall thickness and diastolic function, hemodynamic parameters, heart rate, and ECG characteristics, such as p-wave amplitude and axis, QRS axis, right ventricular hypertrophy, bundle branch block, right ventricular strain pattern and the corrected QT interval (Table 1).

Characteristics of the prospective patient cohort.

Of 64 (52.9%) patients diagnosed with "precapillary PH" (Table 2), 26 had CTEPH, 18 idiopathic or familial PH or PH associated with corrected or small uncorrected atrial septal defect, 13 patients suffered from PH associated with chronic lung disease [31], 3 had porto-pulmonary hypertension, 2 patients suffered from PH in association with collagen vascular disease and 2 patients had PH associated with HIV infection.

Of the 57 (47.1%) patients diagnosed with "no precapillary PH", 32 suffered from postcapillary PH associated with either chronic lung disease [32] or diastolic left ventricular dysfunction, and 25 had normal pulmonary pressures [16]. Patients with normal pulmonary pressures suffered from parenchymal or bronchial pulmonary diseases (n=9), collagen vascular disease (n=3), coronary artery disease (n=2), unilateral occlusion of the pulmonary artery (n=1), isolated tricuspid regurgitation (n=1), patent arterial duct (n=1) or abnormal pulmonary vein drainage (n=1), and seven patients suffered from isolated systemic hypertension.

Predictors of diagnosis.

Based on retrospective patient data, univariable (Table 3) and three separate multivariable logistic regression models (Table 4) were constructed for TTE, clinical parameters and ECG variables. sPAP (OR [95% CI] 1.06 [1.03-1.09], p<0.001), right

ventricular dysfunction (OR [95% CI] 10.28 [2.18-48.44], p=0.003) and the absence of left ventricular hypertrophy (OR [95% CI] 0.34 [0.15-0.75], p=0.008) were identified as independent predictors of "precapillary PH". Of the clinical variables tested, serum NT-proBNP (OR [95% CI] 2.01 [1.21-3.33], p=0.007), $PaCO_2$ (OR [95% CI] 0.86 [0.79-0.93], p<0.001) and associated medical conditions (OR [95% CI] 3.37 [1.04-10.90], p=0.043) remained independent discriminative factors. ECG variables with the strongest diagnostic accuracy were heart rate (OR [95% CI] 1.05 [1.02-1.08], p<0.001) and RVS (OR [95% CI] 52.93 [17.27-162.18], p<0.001).

Accuracy of CART.

Because all patients with sPAP ≥36mmHg and a suspicion of PH were referred to RHC, the sensitivity of TTE was 100%, and the specificity 0.0%. For a more specific non-invasive diagnostic decision tree, all independent clinical and ECG parameters that had been identified in the multivariable logistic regression models (Table 4) were fed into the CART algorithm. The model automatically selected RVS and NT-proBNP for primary decision tree construction (Figure 1).

CART had a sensitivity of 99.4% and a specificity of 40.7%. Because these figures may be too optimistic as they are computed from data the tree had been derived from, two validation steps were added. Internal validation by the bootstrap technique was performed on the original data set resulting in a sensitivity of 97.9% (95% CI: 94.5-99.2%) and a specificity of 17.3% (95% CI: 9.5-29.5%). Temporal validation was performed on data from 121 prospectively recruited patients and yielded a sensitivity of 100% (95% CI: 94.3-100%) and a specificity of 19.3% (95% CI: 11.1-31.3%, Table 5). While sensitivity was unchanged (100% versus 100%, p=1.0), specificity had improved from 0.0% according to current clinical practice, to 19.3% (p=0.0009).

Discussion.

According to current guidelines [2], a significant proportion of patients referred for unexplained dyspnea is undergoing invasive pressure measurements. To test the accuracy of standard non-invasive diagnostic tools, we analyzed data sets from 251 retrospective and 121 prospective patients who underwent RHC for evaluation of PH. The main finding of the present work is that ECG and NT-proBNP on top of TTE suffice to predict significant precapillary pulmonary vascular disease at a level of sensitivity of 100%, and specificity of 19.3%. In practice, based on the CART algorithm, a RHC can be safely withheld in 9% of patients with elevated echo sPAP and clinical PH suspicion without overlooking true PH cases.

PAH, which is one of the major causes of precapillary PH, is a severe condition with serious prognosis [33]. The availability of potent vasodilator therapies that positively impact morbidity and mortality [2, 34] has supported early recognition and treatment [20, 35]. Moreover, screening of asymptomatic individuals at increased risk for PH has been recommended. While invasive hemodynamic assessment has been considered the diagnostic gold standard in PH, TTE is the recommended screening tool [20, 34]. TTE is non-invasive, broadly available and most studies report a high correlation of 0.57-0.93 between TTE and invasive measurements of pulmonary arterial systolic pressures [2]. However, elevated sPAP may result from either precapillary PH or postcapillary PH, which cannot be safely distinguished by TTE alone. In contrast to postcapillary PH [15], precapillary vascular disease is a rare condition [7]. These circumstances have recently led to numerous invasive procedures for exclusion. To narrow the grey zone that is blurring the distinction between pre- and postcapillary disease by echocardiography, current recommendations propose an invasive diagnostic work-up in patients with echocardiographic sPAP values exceeding 50mmHg [36]. According to our

assessments, this diagnostic approach would have substantially increased specificity to 42.1%, however, at the price of overlooking 6.2% of true precapillary PH cases.

Although of limited value, standard ECG has diagnostic [37] and prognostic [38] potential in PH. Despite the fact that postcapillary PH may cause a RVS pattern on ECG [39], RVS remained the strongest predictor of "precapillary PH" in our study. RVS depicts right ventricular electric repolarization, and appears to be a sensitive and immediate marker of right ventricular strain. The presence of RVS correctly identified 78.8% of precapillary PH cases. In addition, several non-invasive prognostic parameters have been established over the past years, e.g., the distance walked in six minutes [40], NYHA functional class [1], $PaCO_2$ [23], associated medical conditions [27, 41-43], and serum NT-proBNP levels [44]. NT-proBNP is released from both cardiac ventricles in response to increased wall tension and is elevated in PH correlating well with pulmonary vascular resistance [45]. Its discriminative accuracy with respect to cardiac versus non-cardiac causes of dyspnea is documented [46], and is primarily based upon its excellent negative predictive value of 96% [47]. The combination of RVS and NT-proBNP, one being a strong positive, the other a strong negative predictor confers clinical usefulness.

A main limitation of our study is its single center design. A center-specific bias with respect to diagnostic procedures, in particular TTE, cannot be excluded. Different referral patterns may influence proportions of PH versus non-PH cases. However, in contrast to positive and negative predictive values, sensitivities and specificities for the detection of PH are independent of the prevalence of healthy individuals in a given cohort.

Taken together, we would like to emphasize that RHC remains the gold standard for the evaluation of PH [11-13]. However, it is widely accepted that a diagnostic procedure that is primarily undertaken to rule out a disease is ideally non-invasive. In a

selected patient population referred for dyspnea and echocardiographic suspicion of PH, integration of the decision tree subsequent to TTE helps to avoid unnecessary RHCs in 9% of cases while not missing a single true PH case.

References.

1. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115(5):343-349.

2. Galie N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J.* 2004;25(24):2243-2278.

3. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G, Begaud B. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996;335(9):609-616.

4. Petitpretz P, Brenot F, Azarian R, Parent F, Rain B, Herve P, Simonneau G. Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. *Circulation.* 1994;89(6):2722-2727.

5. Bonderman D, Jakowitsch J, Adlbrecht C, Schemper M, Kyrle PA, Schonauer V, Exner M, Klepetko W, Kneussl MP, Maurer G, Lang I. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. *Thromb Haemost.* 2005;93(3):512-516.

6. Bonderman D, Wilkens H, Wakounig S, Schafers HJ, Jansa P, Lindner J, Simkova I, Martischnig AM, Dudczak J, Sadushi R, Skoro-Sajer N, Klepetko W, Lang IM. Risk factors for chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2008.

7. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet.* 1998;352(9129):719-725.

8. Bonderman D, Jakowitsch J, Redwan B, Bergmeister H, Renner MK, Panzenbock H, Adlbrecht C, Georgopoulos A, Klepetko W, Kneussl M, Lang IM. Role for staphylococci in misguided thrombus resolution of chronic thromboembolic pulmonary hypertension. *Arterioscler Thromb Vasc Biol.* 2008;28(4):678-684.

9. Jais X, Ioos V, Jardim C, Sitbon O, Parent F, Hamid A, Fadel E, Dartevelle P, Simonneau G, Humbert M. Splenectomy and chronic thromboembolic pulmonary hypertension. *Thorax.* 2005;60(12):1031-1034.

10. Lang IM. Chronic thromboembolic pulmonary hypertension--not so rare after all. *N Engl J Med.* 2004;350(22):2236-2238.

11. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009;54(1 Suppl):S55-66.

12. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J.* 2009;34(6):1219-1263.

13. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, McGregor K, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Al Attar N, Andreotti F, Aschermann M, Asteggiano R, Benza R, Berger R, Bonnet D, Delcroix M, Howard L, Kitsiou AN, Lang I, Maggioni A, Nielsen-Kudsk JE, Park M, Perrone-Filardi P, Price S, Domenech MT, Vonk-Noordegraaf A, Zamorano JL. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009;30(20):2493-2537.

14. Hoeper MM, Barbera JA, Channick RN, Hassoun PM, Lang IM, Manes A, Martinez FJ, Naeije R, Olschewski H, Pepke-Zaba J, Redfield MM, Robbins IM, Souza R, Torbicki A, McGoon M. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *J Am Coll Cardiol.* 2009;54(1 Suppl):S85-96.

15. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography

Associations of the European Society of Cardiology. *Eur Heart J.* 2007;28(20):2539-2550.

16. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med.* 2009;179(7):615-621.

17. Michelakis ED. Soluble guanylate cyclase stimulators as a potential therapy for PAH: enthusiasm, pragmatism and concern. *Eur Respir J.* 2009;33(4):717-721.

18. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, Barst RJ, Ghofrani HA, Jing ZC, Opitz C, Seyfarth HJ, Halank M, McLaughlin V, Oudiz RJ, Ewert R, Wilkens H, Kluge S, Bremer HC, Baroke E, Rubin LJ. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. *J Am Coll Cardiol.* 2006;48(12):2546-2552.

19. Schenk P, Stiebellehner L, Burghuber OC, Kneussl M, Lang IM. [Examination of pulmonary circulation using right heart catheterization. Position paper of the Cardiopulmonary Task Force of the Austrian Society for Pneumology and the Austrian Society for Cardiology]. *Wien Klin Wochenschr.* 2005;117(18):651-662.

20. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, Loyd JE. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126(1 Suppl):14S-34S.

21. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Koerner SK, et al. Primary pulmonary

hypertension. A national prospective study. *Ann Intern Med.* 1987;107(2):216-223.

22. Fijalkowska A, Kurzyna M, Torbicki A, Szewczyk G, Florczyk M, Pruszczyk P, Szturmowicz M. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. *Chest.* 2006;129(5):1313-1321.

23. Hoeper MM, Pletz MW, Golpon H, Welte T. Prognostic value of blood gas analyses in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J.* 2007.

24. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29(19):2388-2442.

25. Braunwald E. *Braunwald's Heart Disease: A textbook of cardiovascular medicine.* 5 ed. Philadelphia; 2004.

26. Burchell HB. The QT interval historically treated. *Pediatr Cardiol.* 1983;4(2):139-148.

27. Bonderman D, Skoro-Sajer N, Jakowitsch J, Adlbrecht C, Dunkler D, Taghavi S, Klepetko W, Kneussl M, Lang IM. Predictors of outcome in chronic

thromboembolic pulmonary hypertension. *Circulation.* 2007;115(16):2153-2158.

28. Hoeper MM, Oudiz RJ, Peacock A, Tapson VF, Haworth SG, Frost AE, Torbicki A. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. *J Am Coll Cardiol.* 2004;43(12 Suppl S):48S-55S.

29. Koenig IR, Malley JD, Weimar C, Diener H-C, Ziegler A. Practical experiences on the necessity of external validation. *Statist. Med.* 2007;26:5499-5511.

30. Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. New York: Chapman & Hall; 1993.

31. Weitzenblum E, Chaouat A, Canuet M, Kessler R. Pulmonary hypertension in chronic obstructive pulmonary disease and interstitial lung diseases. *Semin Respir Crit Care Med.* 2009;30(4):458-470.

32. Funk GC, Lang I, Schenk P, Valipour A, Hartl S, Burghuber OC. Left ventricular diastolic dysfunction in patients with COPD in the presence and absence of elevated pulmonary arterial pressure. *Chest.* 2008;133(6):1354-1359.

33. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Simonneau G. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med.* 2006;173(9):1023-1030.

34. Grunig E, Weissmann S, Ehlken N, Fijalkowska A, Fischer C, Fourme T, Galie N, Ghofrani A, Harrison RE, Huez S, Humbert M, Janssen B, Kober J, Koehler R, Machado RD, Mereles D, Naeije R, Olschewski H, Provencher S, Reichenberger F, Retailleau K, Rocchi G, Simonneau G, Torbicki A, Trembath

R, Seeger W. Stress Doppler Echocardiography in Relatives of Patients With Idiopathic and Familial Pulmonary Arterial Hypertension. Results of a Multicenter European Analysis of Pulmonary Artery Pressure Response to Exercise and Hypoxia. *Circulation.* 2009.

35. Galie N, Rubin L, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet.* 2008;371(9630):2093-2100.

36. Olschewski H, Hoeper MM, Borst MM, Ewert R, Grunig E, Kleber FX, Kopp B, Opitz C, Reichenberger F, Schmeisser A, Schranz D, Schulze-Neick I, Wilkens H, Winkler J, Worth H. [Diagnosis and therapy of chronic pulmonary hypertension]. *Pneumologie.* 2006;60(12):749-771.

37. Ahearn GS, Tapson VF, Rebeiz A, Greenfield JC, Jr. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease. *Chest.* 2002;122(2):524-527.

38. Bossone E, Paciocco G, Iarussi D, Agretto A, Iacono A, Gillespie BW, Rubenfire M. The prognostic role of the ECG in primary pulmonary hypertension. *Chest.* 2002;121(2):513-518.

39. Enomoto H. Clinical Studies on the Ventricular Strain Pattern Electrocardioogram (I) : Clinical Statistical Studies. *Jap Circ J.* 1961;25:1277-1286.

40. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with

cardiopulmonary exercise testing. *Am J Respir Crit Care Med.* 2000;161(2 Pt 1):487-492.

41. Kawut SM, Taichman DB, Archer-Chicko CL, Palevsky HI, Kimmel SE. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest.* 2003;123(2):344-350.

42. Kawut SM, Taichman DB, Ahya VN, Kaplan S, Archer-Chicko CL, Kimmel SE, Palevsky HI, Kawut SM, Taichman DB, Archer-Chicko CL, Palevsky HI, Kimmel SE. Hemodynamics and survival of patients with portopulmonary hypertension. *Liver Transpl.* 2005;11(9):1107-1111.

43. Rich S, Shillington A, McLaughlin V. Comparison of survival in patients with pulmonary hypertension associated with fenfluramine to patients with primary pulmonary hypertension. *Am J Cardiol.* 2003;92(11):1366-1368.

44. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation.* 2000;102(8):865-870.

45. Pruszczyk P. N-terminal pro-brain natriuretic peptide as an indicator of right ventricular dysfunction. *J Card Fail.* 2005;11(5 Suppl):S65-69.

46. Tabbibizar R, Maisel A. The impact of B-type natriuretic peptide levels on the diagnoses and management of congestive heart failure. *Curr Opin Cardiol.* 2002;17(4):340-345.

47. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med.* 2002;347(3):161-167.

Figure legends.

Figure 1. Pulmonary hypertension (PH) diagnosis tree based on the CART algorithm. RVS=right ventricular strain, BNP=N-terminal proBNP.

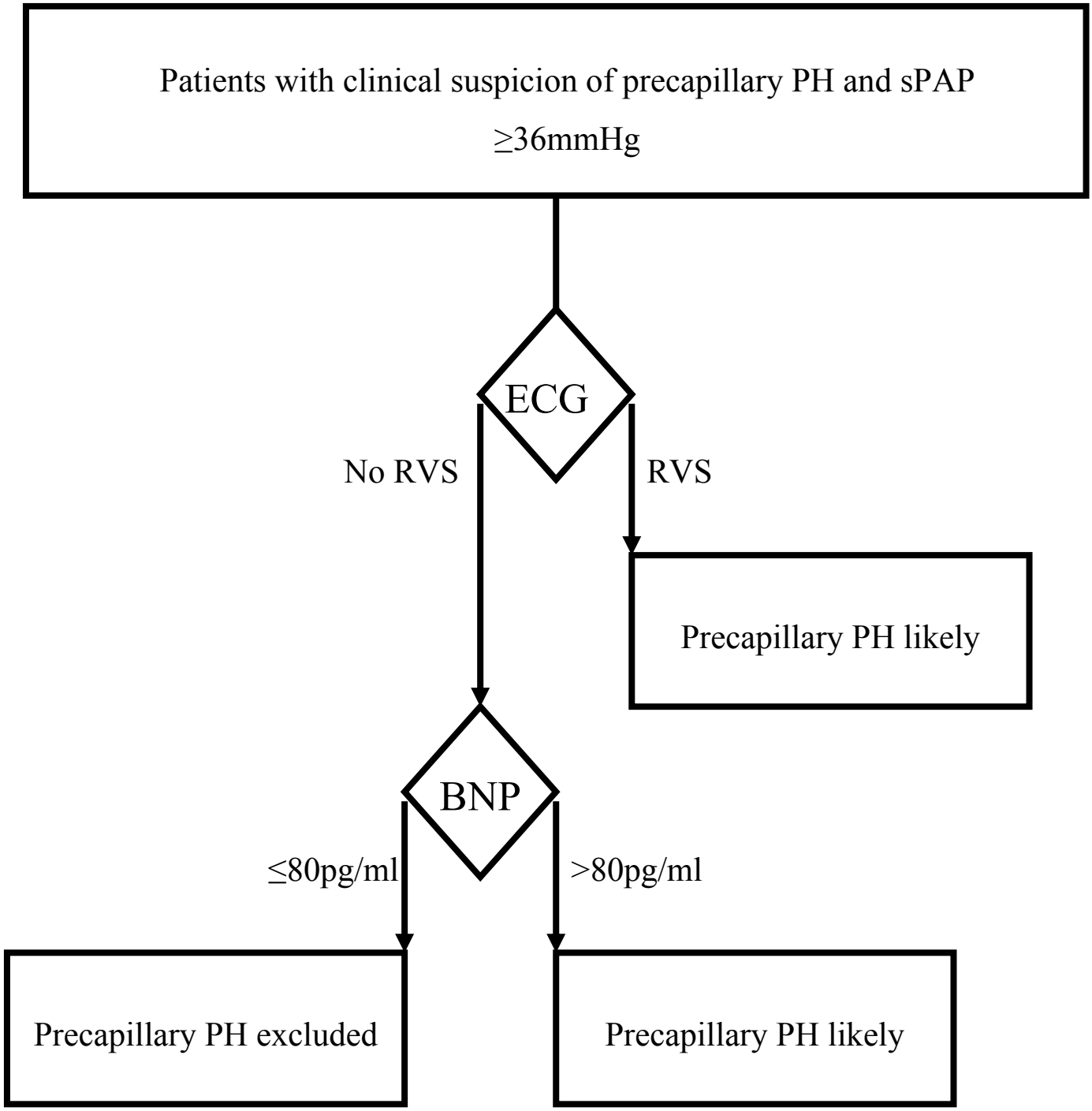

Figure 1

	pPH (n=187)	no pPH (n=64)	p-value
Clinical parameter			
Age (years)	56.3±15.8	60.9±15.5	0.045

Sex (male)	71 (38.0%)	26 (40.6%)	0.77
6-minute walking distance (m)	336±139	367±117	0.15
NYHA classes III+IV	123 (65.8%)	29 (45.3%)	0.005
log Serum NT-proBNP (pg/ml)	1348±1693	478±1055	<0.001
Serum creatinine (mg/dl)	1.1±0.3	1.1±0.3	0.77
$PaCO_2$ (mmHg)	34.5±5.3	37.5±4.3	<0.001
Associated medical condition	52 (27.8 %)	5 (7.8 %)	<0.001
TTE parameter			
Systolic PAP (mmHg)	82.2±27.2	50.0±13.4	<0.001
Right atrial diameter (mm)	58.0±9.5	54.6±8.0	0.012
Right atrial pressure (mmHg)	10.0±4.0	6.8±2.4	<0.001
TR severity (moderate + severe)	81 (43.3%)	17 (26.6%)	0.017
Right ventricular dysfunction	108 (61.4%)	2 (3.2%)	<0.001
Right ventricular diameter (mm)	43.8±8.3	35.0±5.9	<0.001
Left ventricular hypertrophy	48 (28.9%)	31 (50.0%)	0.005
Left ventricular diastolic dysfunction	79 (47.6%)	43 (69.4%)	0.004
Hemodynamic parameter			
Cardiac output (l/min)‡	4.5±1.3	6.0±1.8	<0.001
Mean PAP (mmHg)	49.3±14.0	23.5±7.5	<0.001
PVR (dynes.s.cm^{-5})	751.4±365.3	158.2±86.2	<0.001
PCWP (mmHg)	10.4±5.6	12.6±5.2	0.007
ECG parameter			
heart rate (beats/min)	81.6±15.3	73.2±14.9	<0.001
p amplitude (mV)*	0.21±0.08	0.15±0.05	<0.001
p axis (°)*	64.3±18.0	56.1±22.9	0.019
QRS axis (°)	67.3±64.5	40.5±43.3	<0.001
QRS duration (ms)	102±20	97±19	0.14
Right ventricular hypertrophy†	92 (49,2%)	7 (10.9%)	<0.001
Right bundle branch block	66 (35.3%)	4 (6.3%)	<0.001
Left bundle branch block	2 (1.1%)	8 (12.5%)	<0.001
Right ventricular strain	147 (78.6%)	5 (7.8%)	<0.001
Left ventricular strain	16 (8.6%)	7 (10.9%)	0.62

QT interval (ms)	384±38	390±45	0.32
Corrected QT interval	434±34	424±31	0.041

Table 1. Retrospective clinical, echocardiographic, hemodynamic and electrocardiographic characteristics of patients with precapillary (pPH) and no precapillary PH (no pPH). Values are presented as mean ± standard deviation or count and percentage. TR= tricuspid valve regurgitation, PAP=pulmonary arterial pressure, TTE=transthoracic echocardiography, PVR=pulmonary vascular resistance; PCWP=pulmonary capillary wedge pressure; *19 patients were excluded from p-wave analysis because of atrial fibrillation. † right ventricular hypertrophy was diagnosed when the ratio of R and S in lead V1 was greater than 1. ‡numbers were derived from measurements based on the thermodilution method.

	pPH (n=64)	**no pPH (n=57)**	**p-value**
Clinical parameter			
Age (years)	59.8±15.6	63.7±11.9	0.13

Sex (male)	27 (42.2%)	23 (40.4%)	0.84
6-minute walking distance (m)	325±126	330±126	0.83
NYHA classes III+IV	49 (76.6%)	29 (45.3%)	0.004
log Serum NT-proBNP (pg/ml)	3648±6541	1489±3518	<0.001
Serum creatinine (mg/dl)	1.2±0.6	1.1±0.2	0.23
$PaCO_2$ (mmHg)	36.1±7.2	38.4±5.3	0.049
Associated medical condition	20 (31.3%)	3 (5.3%)	<0.001
TTE parameter			
Systolic PAP (mmHg)	82.6±24.3	55.2±16.3	<0.001
Right atrial diameter (mm)	58.7±10.9	59.1±11.5	0.870
Right atrial pressure (mmHg)	9.5±3.2	8.4±3.5	0.074
TR severity (moderate + severe)	36 (56.3%)	22 (38.6%)	0.016
Right ventricular dysfunction	42 (65.6%)	2 (3.5%)	<0.001
Right ventricular diameter (mm)	44.0±9.2	38.2±6.9	<0.001
Left ventricular hypertrophy	24 (37.5%)	30 (52.6%)	0.39
Left ventricular diastolic dysfunction	31 (48.4%)	42 (73.7%)	0.001
Hemodynamic parameter			
Cardiac output (l/min)‡	4.2±1.1	5.0±1.4	0.001
Mean PAP (mmHg)	46.8±13.4	28.4±11.0	<0.001
PVR (dynes.s.cm^{-5})	736.8±332.0	107.2±121.6	<0.001
PCWP (mmHg)	10.9±5.1	16.5±8.4	<0.001
ECG parameter			
heart rate (beats/min)	85.7±14.6	77.3±18.6	0.007
p amplitude (mV)*	0.19±0.07	0.15±0.06	0.004
p axis (°)*	61.0±29.7	65.3±15.2	0.43
QRS axis (°)	75.3±66.7	48.3±49.5	0.02
QRS duration (ms)	103±20	99±21	0.36
Right ventricular hypertrophy†	37 (57.8%)	9 (15.8%)	<0.001
Right bundle branch block	12 (18.8%)	8 (14.0%)	0.49
Left bundle branch block	0 (0.0%)	1 (1.8%)	0.47
Right ventricular strain	41 (64.1%)	10 (17.5%)	<0.001
Left ventricular strain	12 (18.8%)	8 (14.0%)	0.49

QT interval (ms)	380±39	384±41	0.29
Corrected QT interval	433±31	426±32	0.053

Table 2. Prospective clinical, echocardiographic, hemodynamic and electrocardiographic characteristics of patients with precapillary (pPH) and no precapillary PH (no pPH). Values are presented as mean ± standard deviation. TR= tricuspid valve regurgitation, PAP=pulmonary arterial pressure, TTE=transthoracic echocardiography, PVR=pulmonary vascular resistance; PCWP=pulmonary capillary wedge pressure; *27 patients were excluded from p-wave analysis because of atrial fibrillation; †right ventricular hypertrophy was diagnosed when the ratio of R and S in lead V1 was greater than 1. ‡numbers were derived from measurements based on the thermodilution method.

Clinical parameter	**OR [95%CI]**	**p-value**
Age (years)	0.98 [0.96-1.00]	0.047
Sex (male)	0.89 [0.50-1.60]	0.71

6-minute walking distance (km*)	0.17 [0.02-1.93]	0.15
NYHA classes III+IV	2.32 [1.30-4.13]	0.004
Serum NT-proBNP (ng/ml*)	2.05 [1.31-3.22]	0.002
$PaCO_2$ (mmHg)	0.89 [0.84-0.95]	<0.001
Associated medical condition	4.55 [1.73-11.96]	0.002

TTE parameter	**OR [95%CI]**	**p-value**
Systolic PAP (mmHg)	1.08 [1.05-1.10]	<0.001
Right atrial diameter (mm)	1.04 [1.01-1.08]	0.0113
Right atrial pressure (mmHg)	1.32 [1.19-1.47]	<0.001
TR severity (moderate + severe)	2.36 [1.26-4.42]	0.008
Right ventricular dysfunction	48.44 [11.47-204.61]	<0.001
Right ventricular diameter (mm)	1.18 [1.12-1.24]	<0.001
Left ventricular hypertrophy	0.41 [0.22-0.74]	0.003
Left ventricular diastolic dysfunction	0.40 [0.22-0.75]	0.004

ECG parameter	**OR [95%CI]**	**p-value**
Heart rate (beats/min)	1.04 [1.02-1.06]	<0.001
p amplitude (μV*)	1.01 [1.01-1.02]	<0.001
p axis (°)	1.02 [1.01-1.04]	0.009
QRS axis (°)	1.01 [1.00-1.01]	0.003
QRS duration (ms)	1.01 [1.00-1.03]	0.14
Right ventricular hypertrophy	7.89 [3.42-18.19]	<0.001
Right bundle branch block	8.18 [2.85-23.51]	<0.001
Left bundle branch block	0.08 [0.02-0.37]	0.001
Right ventricular strain	43.37 [16.32-115.26]	<0.001
Left ventricular strain	0.76 [0.30-1.95]	0.57
Corrected QT interval	1.01 [1.00-1.02]	0.043

Table 3. Clinical, echocardiographic and ECG parameters to predict precapillary PH in the retrospective cohort (univariable logistic regression). TR= tricuspid valve regurgitation, TTE=transthoracic echocardiography;

PAP=pulmonary arterial pressure; * units of measurement were adjusted for better readability of confidence intervals.

Clinical parameter	**OR [95%CI]**	**p-value**
Serum NT-proBNP (ng/ml*)	2.01 [1.21-3.33]	0.007
$PaCO_2$ (mmHg)	0.86 [0.79-0.93]	<0.001

Associated medical condition	3.37 [1.04-10.90]	0.043
TTE parameter	**OR [95%CI]**	**p-value**
Systolic PAP (mmHg)	1.06 [1.03-1.09]	<0.001
Right ventricular dysfunction	10.28 [2.18-48.44]	0.003
Left ventricular hypertrophy	0.34 [0.15-0.75]	0.008
ECG parameter	**OR [95%CI]**	**p-value**
Heart rate (beats/min)	1.05 [1.02-1.08]	<0.001
Right ventricular strain	52.93 [17.27-162.18]	<0.001

Table 4. Clinical, echocardiographic and ECG parameters to predict precapillary PH in the retrospective cohort (multivariable logistic regression). TTE=transthoracic echocardiography; PAP=pulmonary arterial pressure; * units of measurement were adjusted for better readability of confidence intervals.

precapillary PH (n)		Predictive parameters			
		RVS	no RVS NT-proBNP>80pg/ml	no RVS NT-proBNP≤80pg/ml	total
diagnosis by RHC	yes	41	23	0	64
	no	11	35	11	57
	total	52	58	11	121

Table 5. Prospective validation of the CART algorithm. These results reflect the true predictive power of the decision tree because the prospectively recruited patients did not contribute to decision tree construction. A total of 121 patients were studied. RVS pattern was present in 52 patients, 41 of whom were diagnosed with "precapillary PH" by RHC. Patients without RVS pattern on ECG (n=69) were further dichotomized according to serum NT-proBNP levels. 58 patients displayed serum NT-proBNP levels>80pg/ml, of these 23 were diagnosed with "precapillary PH". In contrast, none of the 11 patients with serum NT-proBNP≤80pg/ml was diagnosed with "precapillary PH". Numbers (n) represent patients. RHC=right heart catheter, RVS=right ventricular strain.